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Low Backache in a 70-year-old Woman

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History and Physical Examination

A 70-year-old woman presented with a 1-year history of progressive low back pain. The onset was insidious without antecedent trauma. She was earlier seen at another institution, where a sacral lesion was found and a CT-guided needle biopsy was performed twice with inconclusive results. The pain subsequently worsened and was exacerbated by activities, especially flexion of the hip, and was relieved by rest and oral and transdermal narcotics. She had occasional nocturnal pain and paresthesias, radiating in the posterior right lower extremity. She also complained of constipation but did not have any urinary symptoms or rectal bleeding. She denied any constitutional symptoms.

Nine years previously, she had been treated for a rectal adenocarcinoma by a low anterior resection, adjuvant 5-fluorouracil, and radiotherapy (50 Gy with a four-field box technique). She had a 30-pack-years' history of smoking but had quit 10 years earlier. The remainder of her medical history was noncontributory, except for thyroxine supplement for hypothyroidism and multiple episodes of subacute intestinal obstruction.

Her family history was significant for lung carcinoma in her father and son, colon carcinoma in her daughter, and colorectal and breast carcinomas in her sister.

Physical examination showed a woman in pain, who required a walker. She had generalized tenderness over the lumbosacral spine and the right sacroiliac joint. Spine movements were restricted and painful, and lateral flexion and rotations elicited back pain radiating to the right gluteal region. The passive straight-leg-raise maneuver was positive at 20° with sciatic stretch signs on the right side. Right hip rotation elicited pain in the right groin region. Pelvic compression-distraction and Gaenslen's tests were positive on both sides but worse on the right. The right extensor hallucis longus was weak (4/5), but there was no objective sensory loss. Knee reflexes were present bilaterally (2+), but ankle reflexes were absent. Anal reflex and tone were normal. The distal vascular examination was normal.

Her laboratory workup, including CA 19–9™ and CA 15–3® (Fujirebio Diagnostics, Inc, Malvern PA), carcinoembryonic antigen, lactate dehydrogenase, protein levels, parathyroid hormone, serum and urine electrophoresis, immunoglobulins, and calcium and phosphorus levels, were normal except for raised alkaline phosphatase of 164 IU/L (normal, 33–130 IU/L) and erythrocyte sedimentation rate of 32 mm/hour (normal, up to 20 mm/hour). A dual-energy xray absorptiometry scan of the hip obtained 6 months previously showed a bone mineral density of 0.6 g/cm^2 with a T-score of -3.6 and a Z-score of -2.5 below the respective standard deviations.

Because of previously inconclusive biopsy results and unclear diagnosis, radiographs (Fig. 1), CT scan (Fig. 2),

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Each author certifies that his institution has approved the reporting of this case report, that all investigations were conducted in conformity with ethical principles of research, and that informed consent was obtained.

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Fig. 1 An anteroposterior radiograph of the pelvis shows a large ill-defined radiolucent lesion in the sacrum, mostly on the right side, with widening of the sacroiliac joint. Further, fractures in various stages of healing are seen in the bilateral pubic rami and the left ischial ramus. The staples are from the previous biopsy.

Fig. 2 An axial CT scan shows destruction of the right side of the sacrum with attenuation similar to skeletal muscles. No mineralization pattern was seen. The biopsy needle is also seen (the patient is prone).

MRI (Fig. 3), Tc-99m hydroxymethylene diphosphonate (HDP; oxidronate sodium) bone scintigraphy (Fig. 4), and a positron emission tomography (PET) scan had been ordered sequentially at the previous institution and these were available for review when the patient was referred to us.

Based on the clinical history, physical examination, laboratory tests, and imaging studies, what is the differential diagnosis?

Imaging Interpretation

An anteroposterior radiograph (Fig. 1) of the pelvis showed a large ill-defined radiolucency in the right sacrum with widening of the sacroiliac joint. Moreover, fractures in various stages of healing were seen in both superior pubic rami and the left inferior pubic ramus. CT

Fig. 3A–C MRI shows a 8.3- × 6.8- × 3.5-cm diffuse abnormal marrow replacement in the sacrum, more on the right side, with a signal isointense to muscles on T1-weighted (**A**) axial (TR 600, TE 13) and (**B**) coronal (TR 750, TE 16.9) images. There is involvement of the sacroiliac joint, as well as the adjoining ilium, with foraminal effacement of the S1–3 nerve roots. (**C**) The lesion enhances heterogeneously with contrast.

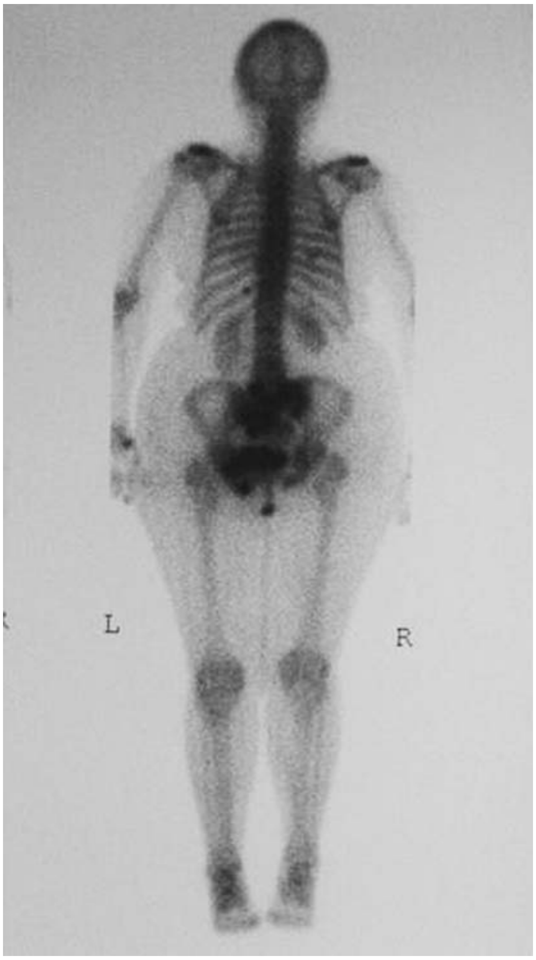

Fig. 4 A Tc-99m HDP bone scan (posterior view) shows an asymmetrical irregular uptake in the sacrum, more on the right side, as well as the pubic rami.

showed apparent destruction of the right hemisacrum and replacement with soft tissue attenuation material equal to that of the adjacent muscle (Fig. 2). No mineralization was seen. MRI revealed a 8.3- × 6.8- × 3.5-cm area of marrow replacement in the right sacrum, with a signal that was isointense to muscle on T1-weighted axial (Fig. 3A; TR 600, TE 13) and coronal (Fig. 3B;TR 750, TE 16.9) images and hyperintense on short tau inversion recovery sequences (TR 4000, TE 10.1). There was involvement of the sacroiliac joint, as well as the adjacent ilium, with foraminal effacement of the S1–3 nerve roots. The lesion enhanced heterogeneously with contrast (Fig. 3C). A Tc-99m HDP bone scan showed asymmetric irregular uptake in the sacrum, more on the right side (Fig. 4), as well as the pubic rami. A PET/CT scan showed increased uptake of 18F-fluorodeoxyglucose in the same area.

Differential Diagnosis

- Metastatic colorectal carcinoma
- Second primary bone tumors (including multiple myeloma, lymphoma, giant cell tumor, chordoma)
- Radiation-induced sarcoma
- Postradiation osteoporotic insufficiency fracture
- Hyperparathyroidism
- Chronic infection (including tuberculosis)

Because the patient had CT-guided needle biopsy on two previous occasions with inconclusive results, an open biopsy was performed to mitigate potential sampling error and histology obtained (Fig. 5).

Based on the clinical history, physical examination, laboratory tests, imaging studies, and histologic picture, what is the diagnosis and how should this lesion be treated?

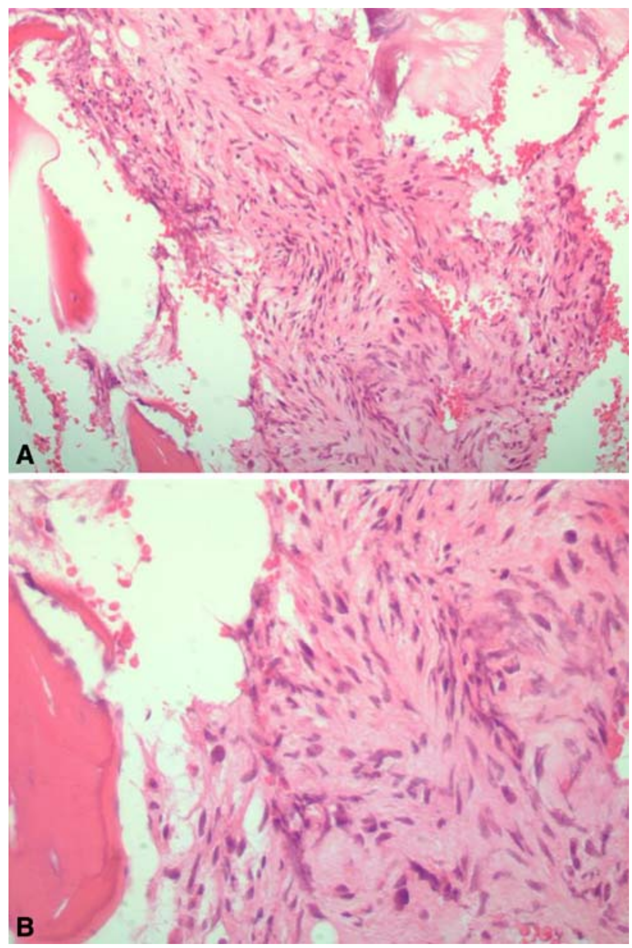

Fig. 5A–B Photomicrographs of hematoxylin and eosin-stained biopsy tissue show fibrosis, hemorrhage, and no inflammation (**A**: original magnification, ×200; **B**: original magnification, ×400). There is no evidence of malignancy.

Histology Interpretation

All biopsies showed a benign, relatively hypocellular lesion with occasional spindle cells, dense stroma, extensive fibrosis, hemorrhage, and no inflammatory component (Fig. 5). The spindle cells had the histologic appearance of myofibroblastic cells with their plump nuclei and modest amounts of amphophilic cytoplasm. The variable cellularity of the spindle cell component and its cytologic blandness pointed to its reactive nature and was not consistent with neoplasia. No mitotic activity or malignant features were seen. Immunohistochemistry for cytokeratin to rule out metastatic rectal adenocarcinoma was negative.

Diagnosis

Postradiation osteoporotic insufficiency fracture.

Discussion and Treatment

Although the radiographic features were atypical and concerning in this patient given her medical and family histories, the diagnosis was postradiation osteoporotic insufficiency fracture. This was based on the history of radiation, her osteoporotic status, unremarkable laboratory workup, no other focus of disease, and improvement on bisphosphonates, calcium, and vitamin D. The clinical findings were supported by the imaging studies showing resorption and widening of the sacroiliac joint and insufficiency fractures in the rami, all in the field of radiation. The microscopic findings were also consistent with an insufficiency fracture.

Radiation-induced osseous changes are favored over an aggressive neoplasm in the absence of soft tissue mass and the presence of stable changes on serial radiographs, sharply defined borders, and multiple lesions limited to radiation-treated tissues [12, 17, 27]. Metastatic disease disseminates hematogenously and gives rise to localized lytic or mixed lytic-sclerotic areas in a normal-appearing bone with a wide zone of transition between normal and abnormal bone. Metastases may extend from bone into the soft tissue and are frequently multicentric [32]. Abnormal laboratory values and a deteriorating clinical course are also present. Metastatic disease is rare in a radiated field [5] and tends to cause a random pattern of scintigraphic uptake throughout the skeleton [16, 18]. A PET scan, although reported to differentiate between recurrence and radiation changes in brain tumors [25], was not helpful in this case. A second bone malignancy with distinctly different histopathologic features compared with the original cancer may be present in up to 20% of the patients with skeletal metastases, especially after breast and prostate primaries [7]. Second malignancies usually appear with a soft tissue mass adjacent to the bone, and a biopsy or bone marrow examination may be necessary. Insufficiency pelvic fractures may also occur in patients with multiple myeloma [11]. Giant cell tumors of the sacrum are usually eccentric and efface the joint or may even cross it. Giant cell tumors of bone are often destructive and nonmatrix-forming with an associated soft tissue mass. They are heterogeneous on MRI with areas of hypointense signal on T1 and T2 pulse-weighted sequences attributable to the high hemosiderin content. They are more frequent in women, with a peak incidence between the third and fifth decades of life. Chordomas, in contrast, are more central, do not efface or cross the joint, and are often associated with a large anterior-based soft tissue mass.

Radiation-induced sarcomas occur in fewer than 0.1% of patients who receive radiotherapy and survive 5 years [21, 34]. Osteosarcomas, pleomorphic undifferentiated sarcomas, fibrosarcomas, angiosarcomas, and chondrosarcomas are the most common radiation-induced histologic subtypes [10, 21]. For a tumor to be classified as radiation induced, certain criteria must be met: the lesion must arise in the radiated field, the histologic features must be different from those of the primary tumor, and the time between radiation and the secondary tumor should be sufficiently long (usually more than 10 years but may range from 2 to 55 years) [6, 16, 21, 35]. Bone destruction with soft tissue extension is common with or without matrix formation. An area in a previously irradiated bone showing expansion or an area of lucency that is larger than the background pattern of radiation change in a bone is suspect [21]. A soft tissue density in marrow other than fat in an irradiated bone may be an early indicator of sarcomatous degeneration [21].

Patients with hyperparathyroidism (primary or secondary including osteomalacia and renal osteodystrophy) often have a Looser zone but will also present with other features, such as decreased mineralization, coarsened texture of the bones, rugger jersey spine, other bone lesions and deformities, and abnormal laboratory values, including serum calcium, phosphorus, alkaline phosphatase, and parathyroid hormone. Infections like tuberculosis may cross the sacroiliac joint and show an area of photopenia on bone scintigraphy (cold abscess). A soft tissue component is common, but metachronous or synchronous involvement of other bones such as the pubis is unusual in an immunocompetent patient. Pathologic and microbiologic studies will further aid in diagnosis.

Stress fractures may be either fatigue or insufficiency type. A fatigue fracture is caused by the application of abnormal stress to a bone with normal elastic resistance, while an insufficiency fracture occurs with a normal or physiologic stress on a mineral-deficient or decreased elastic resistance bone [9]. Since its first description in 1982 [23], insufficiency fractures of the sacrum remain an unsuspected, but not uncommon, cause of low back pain in an elderly population [8]. The diagnosis may be difficult for several reasons [8, 20]. First, the findings on routine radiographs may be subtle and may be overlooked owing to the complex anatomy and overlying bowel shadow and calcification. They have often been interpreted as normal, even retrospectively, in greater than ½ of the cases [15]. Stress fractures through cancellous bone, especially in an osteopenic skeleton, are difficult to detect [20]. Second, metastatic disease is often suspected based on the clinical and radiographic findings, especially in a patient with a known history of malignancy. Third, a biopsy specimen from an insufficiency fracture may contain immature bone, cellular stroma, necrotic debris, and inflammation. These histopathologic findings, out of context, may be interpreted as a sarcoma or osteomyelitis [9].

The diagnosis of insufficiency fracture depends on careful clinical, pathologic, and radiographic correlation and should be suspected in elderly patients with osteopenia or individuals with a prior history of radiation exposure to the area. Typically, the fracture is vertical in the sacral alae and oriented parallel to the sacroiliac joint. Transverse fractures develop secondarily and can displace with time. They may also be located just lateral to the margins of the lumbar spine. This distribution suggests the weight of the body transmitting through the spine to the pelvis may be at least partially responsible for the fracture [8]. The presence of additional fractures in the spine or pelvis (up to 80% and mostly in the pubis), especially with a history of local radiotherapy, helps confirm the pathologic process in the sacrum is indeed a fracture [4, 5, 8, 11, 20, 27, 36]. Bilateral or multiple pelvic fractures can result in delayed healing [4, 5]. Bone scintigraphy is the most sensitive study and commonly shows an H-shaped increased uptake (Honda sign) in up to 45% of cases (although other patterns have also been described) [9, 15, 20, 28, 30, 32]. CT, with proper window setting, further confirms and defines the fracture and excludes a destructive process [9]. MRI findings are nonspecific but helpful in showing early medullary edema, fracture lines, and the absence of a soft tissue mass [9]. Extensive bone resorption attributable to insufficiency fracture has been described in the pubis, ribs, and clavicle [11, 18, 21, 26], but not in the sacrum as noted in this case.

Radiation-induced atrophy of the bone is dose related and occurs when the dosage exceeds 40 Gy [13, 16, 21, 27]. Technical aspects of radiotherapy that increase the risk of insufficiency fracture include the number of fields treated per day, use of orthovoltage therapy, and delivery of high daily dose per fraction [16, 27]. The time between radiation therapy to fracture diagnosis ranges from 2 weeks to 8 years and is unpredictable [13, 24, 28], although most occur within the first 3 years [13]. Although less common with megavoltage therapy, skeletal changes in the pelvis after local radiation have been described in the sacrum, hip, pubic rami, pubic symphysis, ilium, and lower lumbar spine [13, 27, 29]. Pelvic insufficiency fractures may occur in as many as 34% of cases after local radiation, depending on diagnostic criteria and the radiotherapeutic modality used [1]. In a recent retrospective cohort study [2], women older than 65 years who underwent local radiation had a higher incidence of pelvic fractures than women who had no radiotherapy. The incidence was higher for anal carcinoma than rectal or cervical carcinoma, with cumulative 5-year fracture rates of 14%, 8.7%, and 8.2% and hazard ratios of 3.2, 1.7, and 1.7, respectively. In contrast, this risk was not substantial for spine or upper extremity fractures.

The highest-risk populations for sacral insufficiency fractures are women who are postmenopausal, have osteoporosis, and receive local radiation. Other predisposing factors include corticosteroids, thyroid hormone replacement, connective tissue disorders, obesity, multiparity, diabetes mellitus, metabolic bone disease, fibrous dysplasia, Tarlov's cyst, spine deformities, THA, excessive pelvic anteversion, and even pregnancy and lactation [3, 9, 15–20, 22–24, 26–33]. Sacral insufficiency fractures in men are uncommon and are reported in less than 8% of cases [15, 36]. Although more common in elderly patients, it can occur in young patients as well and has been described in individuals as young as 8 years old [14].

The most common presentation is severe back or buttock pain, reported in 64% and 43% of patients, respectively, although up to 22% of patients are believed asymptomatic at diagnosis [1]. Antecedent minor trauma was reported in 32% of cases [15]. Approximately 80% of patients complain of sacral tenderness and 14% have neural symptoms [15]. Additionally, these patients may have radiation-induced hematuria, rectal bleeding, or bowel obstruction [29].

Most patients with pelvic insufficiency fractures respond to simple nonoperative modalities and become pain-free within a year. After a short period of bed rest and analgesics, management consists of gradual mobilization and antiosteoporotic treatment [18, 22, 29, 33]. Improvement and resolution usually occur between 2 weeks and 24 months (up to 131 months) and depend on the cause and associated fractures [15].

The diagnostic dilemma in patients with radiation-induced sacral fractures arises from the fact that the treatment of primary malignancy promotes the development of a condition that simulates metastasis or primary osseous malignancy. Awareness of this entity should

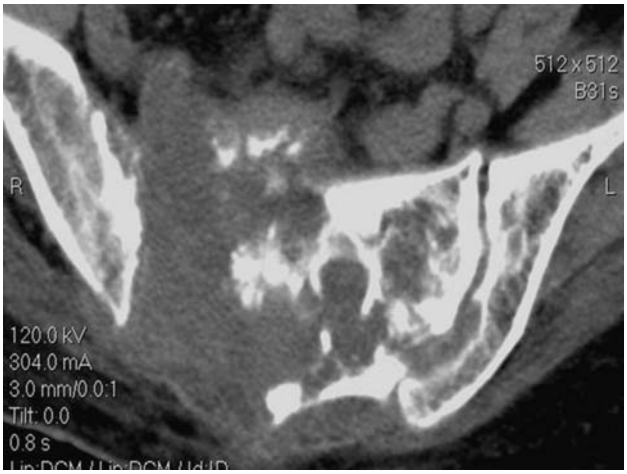

Fig. 6 A comparative axial CT scan at 4 months' followup shows little additional mineralization in the lesion with no further bone destruction.

prevent confusion with metastatic disease and unnecessary tests to diagnosis and treat this condition. Occasionally, however, in some patients, a biopsy and/or serial radiographic studies may be necessary to confirm the diagnosis. Biopsy should be performed judiciously as the biopsy can result in infection and irreparable devitalized bone [4, 5]. The elderly woman with a history of pelvic radiation is at greatest risk for sacral insufficiency fracture [24].

Our patient was treated initially with bed rest for 6 weeks with in-bed spinal exercises. This was followed by gradual mobilization with assistive devices and physiotherapy, including gait training for 3 months. She was also treated for her underlying osteoporosis with bisphosphonates, calcium, and vitamin D supplements throughout. Her pain gradually improved and was considerably better by 3 months. A CT scan at 4 months did not show substantial improvement, although some increased mineralization of the lesion was evident (Fig. 6). At 5 months' followup, she had occasional discomfort on prolonged sitting, standing, or walking, requiring use of a single cane. Followup of her rectal carcinoma remained unremarkable.

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